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Optimization of an herbicide release from ethylcellulose microspheres

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Summary

The herbicide 2,4-D was microencapsulated using ethyl cellulose to develop controlled release formulations that protect it from photodegradation and evaporation and to reduce the environment pollution. Ethyl cellulose microspheres loaded with 2,4-D were prepared by the emulsion solvent-evaporation technique. We have obtained the desired microspheres with higher drug entrapment and encapsulation yield by varying certain conditions as stirring speed, polymer-solvent ratio, drug-polymer ratio, pH of continuous phase and organic phase solvent. The shape and size of microspheres were analysed by scanning electron microscopy. The herbicide release was studied at 25°C and the release data were analysed according to Fick's Law. The results demonstrate that we can control the release rate by modifying the process parameters.

Introduction

Applied by conventional methods, pesticides are invariably subject to leaching, evaporation and degradation (photolytic, hydrolytic and microbial); then to reduce their toxicological impact on the environment, enormous progress and formulation research have been made [1-3]. For the production of controlled release agricultural formulations microencapsulation technologies are the most used [4-5], as well, this process is applied in other fields [6-7]. The encapsulation process can prolong the active life of pesticide by providing a timed release of active ingredient which improves work efficiency. Also among the purposes of pesticide formulations are to get higher safety, higher efficacy and labour-saving; these formulations make handling and application of pesticides easy and safer for workers and users, reduce harmful effects on non-target organisms and environment. Microencapsulation can be carried out by different techniques [8] which allow to two types of system: microcapsules and microspheres. The last one where the core material is dispersed in the matrix can be obtained by solvent evaporation technique [9]. This popular process of microencapsulation can be readily performed in the laboratory without the need for specialised equipment. It has been used to formulate different biological core materials [10-11] and particularly the pesticides such as Dicamba [12] and norfluazon [13]. Some matrixes have been used to prepare controlled release herbicide

formulations such as alginate gels [12, 14-17], acrylic and methacrylic polymers [18], starch [19] and ethylcellulose and polyarylsulfone [12]. In O/W emulsion solvent evaporation, several parameters which can influence the properties of microspheres and the encapsulation effectiveness were identified. Therefore optimisation of the process parameters may be advantageous. Jones and Pearce [20] have studied some factors such as pH of external phase, stabiliser concentration and the stirring on the drug loading percentage. Chung and al. were studied by the rate of solvent evaporation and its influence on the microspheres morphology, encapsulation efficiency and the drug release [10].
Among the herbicides with potential toxicity against humans are phenoxy compounds such as 2,4-D (2,4-Dichlorophenoxyacetic acid), 2,4,5-T (2,4,5-trichlorophenoxy acetic acid), MCPA (4-chloro-2-methylphenoxyacetic acid) and their esters [21-22]. The 2,4-D is the most widely used herbicide in the world (Industry Task Force Research Data) for weed control in cereals and other crops. As a result of its wide usage, 2,4-D may contaminate groundwater, streams and rivers due to spraying, spills, leaching and runoff. In the present investigation, 2,4-D and ethyl cellulose were used as core material and water insoluble polymer, respectively, for the preparation of controlled release formulations "microspheres". These formulations have potential to reduce the surface run-off and leaching of soil-applied herbicide and decrease the amount of herbicide being applied to the soil and also to reduce the enzymatic photodegradation of 2,4-D. 2,4-D has been formulated by other process : chemical reaction [23-24] or incorporation method [17]. In present study, the goal is to link up the process control parameters of microencapsulation and factors controlling the drug release. For this and using solvent evaporation technique, some process parameters have been studied like stirring speed, stabiliser concentration, polymer concentration, drug-polymer ratio, pH of external phase and internal phase solvent. The influence of these factors on the drug loading and drug release were investigated. In the end, the influence of pH of release medium were also studied.

Materials and methods

Preparation of microspheres

Encapsulation reactor
Microspheres were prepared in cylindrical glass reactor (600ml, ∅=80mm) with six-blade turbine impeller (blade length=50mm, blade width=10mm, type IKA RW 20 DZM.n).

Preparation
The method of preparation of microspheres is based on the emulsion-solvent evaporation technique. 2,4-D was dispersed in 32g of DCM or dissolved in 32g of DCM/Acetone mixture (90:10, w/w), then ethylcellulose was added and the mixture was heated with light reflux (30-35°C) and stirring during one hour. At the same time, PVA used as stabiliser was dissolved in 250g of deionized water under heating and stirring. After cooling to room temperature, organic phase was emulsified with aqueous medium under stirring for 5-6hours. The dispersion was filtered and microspheres were vacuum dried in dessiccator in presence of $CaCl_2$.The formulation parameters selected and varied are: stirring speed (N) of emulsion, polymer-solvent (%Pol./solv.:%w:w), drug-polymer (%2,4-D/Pol.: or %2,4-D_i), stabiliser-water (%PVA, %w:w) ratios and aqueous phase pH (5,5 and 1.1).

UV spectoscopy analysis

To determine drug loading and drug release, the drug concentration were obtained using UV-Vis spectrophotometer (JASCO –530) at λ_{max} =229nm of 2,4-D and corresponding experimental coefficients of $\varepsilon(\varepsilon_{at\ pH=5.5}$=10255.8 $l.mol^{-1}.cm^{-1}$, $\varepsilon_{at\ pH=9.1}$=8633.8 $l.mol^{-1}.cm^{-1}$ and $\varepsilon_{\ in\ ethanol}$=10971.0 $l.mol^{-1}.cm^{-1}$).

Characterization of microspheres

Drug content

The dried microspheres (50mg) were dissolved in 20ml of absolute ethanol under shaking in corked bottle during 4hours. The resulting solution were analysed before appropriate dilution with ethanol by UV spectroscopy. Extraction was performed in triplicate. The loading percentage of drug and the encapsulation yield were calculated by the following equations:

Loading percentage:

$$\%2{,}4-D_{loaded}=\frac{weight.of\ .pesticide.in.microspheres}{weight.of\ .loaded.microspheres}.100 \quad (\mathbf{1})$$

Encapsulation yield %:

$$Yield=\frac{weight.of\ .pesticide.in.microspheres}{initial.weight.of\ .pesticide}.100 \quad (\mathbf{2})$$

Scanning electron microscopy

The surface characteristics were observed and photographed by means of scanning electron microscopy. The microspheres were deposited on carbon film and then samples were examined with scanning electron microscope (Hitachi S3000) at 70Pas and 5°C under 12Kv of acceleration tension.

Size and size distribution

The mean diameters and size distribution were calculated from the results of optical microscopy (Vickers instruments), by a counting of more than 500 microspheres using appropriate lenses. By the mean of Excel spreadsheet we have determine the size and size distribution of microspheres. We should be indicate that we have used this long and trying method and not laser diffract meter in order to avoid counting aggregate microparticles.

Release studies

Dissolution reactor

The release kinetics of the active agent from ethylcellulose microspheres were done in stopped Erlenmeyer flask as shown in figure 1. This reactor was chosen in order to withdraw solution without microparticles. At desired time, the sample is taken from solution which is rise into the filter tube when cap 1 is removed.

At initial time, microspheres were soaked in dissolution reactor containing 1000g of deionized water (pH=5.5) or basic medium (pH=9.1) as release media. The dissolutions were conducted in a bath with temperature and stirring rate of 25°C and

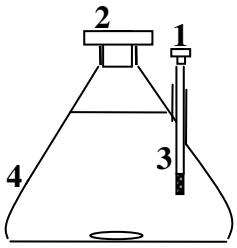


Figure 1: dissolution reactor: 1,2: caps; 3: filter tube; 4: Erlenmeyer flask.

250rpm respectively. At the sampling times, 3ml of solution were withdrawn from filter tube and analysed by UV spectroscopy and then re-put in the dissolution medium.

Release data analysis

The release of the herbicide involves 4 stages:

(i : penetration of water into microspheres
ii : diffusion of water and dissolution of herbicide
iii : diffusion of herbicide into polymer
iiii : transfer of active agent in solution).

But the whole process is probably governed by the slowest step, ie diffusion of the herbicide throughout microspheres.

Therefore, the release of herbicide can be described by the basic equation for unsteady state diffusion called Fick's second law. If we suppose that microspheres of radius R are isotropic, the equation of diffusion of active agent into polymeric matrix is :

$$\frac{\partial C}{\partial t} = \frac{1}{r^2}\frac{\partial}{\partial r}\left[Dr^2\frac{\partial C}{\partial r}\right] \qquad o < r < R \qquad (\mathbf{3})$$

C is concentration, D diffusivity and r the distance. The solution of equation (1) depends on initial and boundary conditions. Bu the cumulative amount of the active agent M_t released in the earlier stages of the process is always [25] given by

$$\frac{M_t}{M_\infty} = 6\left(\frac{Dt}{\Pi R^2}\right)^{1/2} = K\, t^{1/2} \qquad (\mathbf{4})$$

where M_∞ is the total amount released at equilibrium. The result is analogous to Higuchi law that states that M_t is proportional to $t^{0.5}$ if we suppose that K is constant.

Chemicals

2,4-Dichlorophenoxyacetic acid (2,4-D), from ACROS Organics , used after grinding in mortar; Ethylcellulose (48%ethoxylate (m/m) EC100, viscosity 0.100 Pa .s at 5% (m/m), in 80/20 toluene/acetone solution), from Aldrich; Polyvinyl alcohol (PVA 88% hydrolysed, Mw=22kD); Dichloromethane (DCM); Acetone 99%, from ACROS Organics, Ethanol absolute 99% from SDS, used as received. Acidic solution at pH=1.1 prepared with Chlorhydric acid (0.1M, for continuous phase). Fresh solution of natrium hydroxyde at pH=9.1 (10^{-5}M, for release medium).

Results and discussion

Microspheres morphology and size

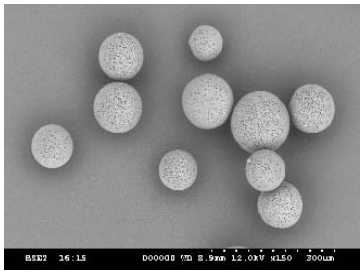
Figures 2 (A-E) show the different SEM photographs of 2,4-D loaded microspheres. All ethylcellulose microparticles obtained were spherical with rough and porous surface. The cross-section in figure2-C shows porous interior aspect of microsphere.

Experimental results, namely, mean diameters, %2,4-D loaded and yields are listed in table 1. From optical microscopy, the particle size depends on the process parameters. The results demonstrate that the mean diameter increases with factor of 3.1±0.3 when we double polymer-solvent ratio.
In the same conditions (%2,4-Di=25.33%, %PVA=0.25%, pH=5.5, DCM) and different stirring speeds (N), relationship was obtained between $\ln(D_{32})$ and $\ln(N)$. Figure 3 illustrate the straight lines with slope of -0.75 and -0.63 at %Pol.=4.68% and 2.34% respectively, when mean diameter of Sauter D_{32} is in µm and N in rpm. This is in agreement with inertial break-up theory [26-27] but the values of slope are different to the theorical one (-6/5). In fact other authors have obtained the same deviation [28-29].
The influence of pH continous phase and organic solvent on the particle size is not notable. However, %PVA should decrease the mean diameter.
In the basis of these results we can say that the polymer-solvent ratio and stirring speed are the most parameters which affect the mean diameter.

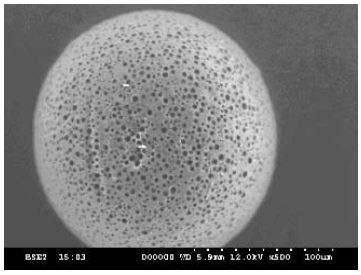
Table 1: Effects of preparation parameters on microsphere sizes, 2,4-D loading and encapsulation yield.

Process parameters											
%2,4-D /Pol.	%pol. /solv.	N (rpm)	Solvent	pH	% PVA	D_{10} (µm)	D_{32} (µm)	D_{43} (µm)	δ	%2,4-D loaded	Yield
25.33	2.34	300	DCM	5.5	1%	88.3	118.0	125.5	1.42	7.77± 0.92	31.80± 3.70
25.33	2.34	200	DCM	5.5	0.25	175.3	220.9	231.9	1.32	10.20± 0.04	42.47± 0.17
25.33	2.34	300	DCM	5.5	0.25	104.4	125.7	132.6	1.27	10.36± 0.70	43.50± 3.30
25.33	2.34	600	DCM	5.5	0.25	75.0	93.3	100.8	1.35	10.05± 0.67	41.33± 2.78
25.33	2.34	800	DCM	5.5	0.25	56.6	87.7	87.6	1.55	10.52± 0.57	41.53± 2.27
25.33	4.68	200	DCM	5.5	0.25	542.9	743.5	796.4	1.47	13.91± 0.71	55.64± 2.70
25.33	4.68	300	DCM	5.5	0.25	280.4	422.4	461.1	1.65	13.04± 0.30	52.60± 1.50
25.33	4.68	600	DCM	5.5	0.25	186.5	283.6	313.8	1.68	14.00± 0.10	54.20± 4.70
25.33	4.68	800	DCM	5.5	0.25	135.1	248.4	284.5	2.11	14.11± 0.17	53.29± 0.70
25.33	2.34	300	DCM	1.1	0.25	80.7	118.5	125.8	1.56	14.39± 2.36	62.79± 8.12
25.33	4.68	300	DCM	1.1	0.25	362.2	450.5	481.7	1.48	18.70± 1.09	78.73± 4.59
25.33	2.34	300	DCM/Ac	5.5	0.25	110.7	139.0	146.5	1.32	12.71± 1.60	47.40± 3.79
25.33	4.68	300	DCM/Ac	5.5	0.25	333.5	449.2	489.1	1.47	16.30± 0.03	68.64± 0.10
25.33	2.34	300	DCM/Ac	1.1	0.25	116.9	136.1	142.6	1.22	17.57± 0.68	67.22± 2.62
25.33	4.68	300	DCM/Ac	1.1	0.25	288.1	401.5	431.2	1.55	19.33± 0.70	81.38± 3.26
50.66	2.34	300	DCM/Ac	5.5	0.25	95.9	121.4	127.1	1.33	17.57± 0.05	41.21± 0.12
50.66	4.68	300	DCM/Ac	5.5	0.25	271.8	359.1	386.2	1.42	23.67± 1.30	57.88± 3.35
50.66	2.34	300	DCM/Ac	1.1	0.25	114.6	129.6	135.4	1.18	20.24± 0.36	51.37± 0.93
50.66	4.68	300	DCM/Ac	1.1	0.25	292.9	376.0	409.5	1.40	27.74± 1.92	70.09± 4.86

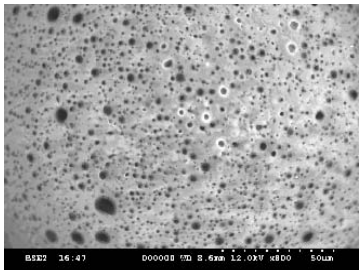
D_{10}: mean diameter in number = $\Sigma n_i d_i / \Sigma n_i$. D_{32}: mean diameter in surface = $\Sigma n_i d_i^3 / \Sigma n_i d_i^2$.
D_{43}: mean diameter in weight = $\Sigma n_i d_i^4 / \Sigma n_i d_i^3$. δ : Dispersion = D_{43}/D_{10}.
(n_i number of microparticles with a mean diameter of d_i).



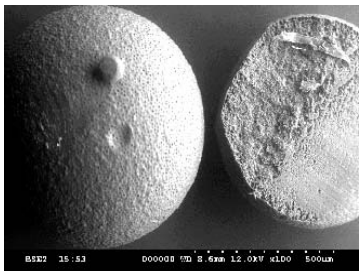
A
x150



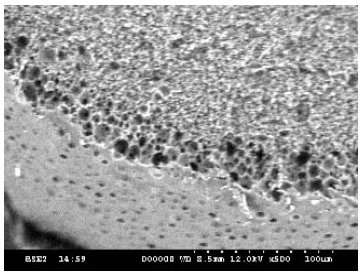
B
x 500



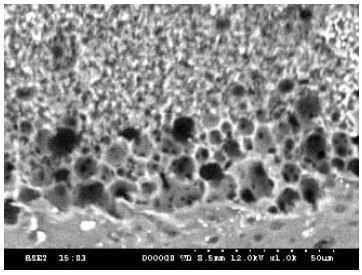
C
x 800



D
x 100



E
x 500



F
x1000

Figure 2: SEM micrographs of ethylcellulose microspheres loaded by 2,4-D (%2,4-Di=25.33%; %PVA=0.25; pH=5.5, DCM).
A, B, C: %Pol. = 2.34%, N=300rpm; D, E, F: %Pol. = 4.68%, N=200rpm.

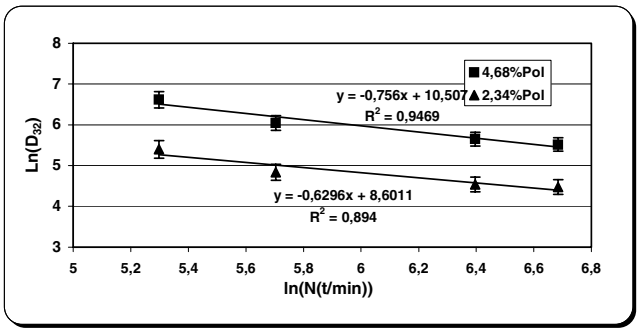


Figure 3: Relationship between the mean diameter of Sauter (D_{32}) and the stirring speed.

Drug loading

In order to obtain optimal efficacy, an increase in loading percentage by adjusting formulation and process variables is needed. The effect on the drug loading of each parameter studied is described below :

Effect of PVA: PVA was used as dispersing agent in the preparation of oil in water emulsions. It was observed that 0.25% of PVA is sufficient to obtain spherical and individual microparticles. If PVA concentration was increased from 0.25% to 1% the drug loading decreased accordingly from 10.10 to 7.77%. Therefore, we have maintained this rate for all the next experiments.

Effect of Stirring speed: experiments were carried out at four stirring rates 200, 300, 600 and 800rpm. The results revealed that drug loading was not affected by stirring speed. For example, if the stirring speed was increased from 200 to 800 rpm the drug loading decreased from 10.20 to 10.52%. Other authors [30] have obtained important effect of the stirring speed on ethylbenzoate loaded in ethylcellulose microspheres. Then we should be thought that the effect of this parameter on drug loading depends on the physico-chemical properties of drug especialy surface tension.

Effect of Polymer percentage : If polymer percentage was increased from 2.34 to 4.68% the drug loading increased from 10.05 to 14.00%. So, at higher polymer concentration in organic phase, drug mobility becomes weak and its migration toward continuous phase is reduced during solvent evaporation. This fact improves the drug entrapment.

Effect of pH of continuous phase: 2,4-D is an acidic herbicide (pKa ≈3 at 25°C) and it exhibits poor aqueous solubility at pH lower than pKa (311mg/l at pH=1 and 25°C) while at pH=5 (where the preponderant species is anionic form), 2,4-D solubility is 2003mg/l. Therefore, we have used acidic continuous phase at pH=1.1 where 2,4-D solubility is weak. In this case the equilibrium is transferred in way of increasing drug entrapment. We have obtained in this condition a higher drug loading percentage. Indeed, if pH was decreased from 5.5 to 1.1 the drug loading increased from 10.05 to 14.39%.

Effect of organic phase solvent: in the first experiments we have only used DCM as solvent in organic phase, so, in this medium, 2,4-D is partially soluble, therefore it is dispersed in polymer solution. Using acetone as co-solvent where 2,4-D is readily soluble, we have obtained a solution of drug and polymer in DCM/Acetone mixture. In this case, drug is lodged inboard polymer structure and when the solvent

evaporates, polymer solidifies involving the entrapment of drug in microsphere. However, the drug loading is not improved significantly. Indeed according to the results from table 1, if we used DCM or DCM/Ac (the other parameters being the same)the drug loading is respectively 18.70% or 19.33%. We think that because acetone is water soluble solvent and it should diffuse quickly toward aqueous phase, and then it can leads the drug out.

Effect of drug-polymer ratio: microspheres with higher drug content were obtained when we have increased the drug-polymer ratio to 50.66%. In fact, we can improve the drug loading by increasing initial concentration of drug but the encapsulation yield is underprivileged; that can be seen in figure 4.

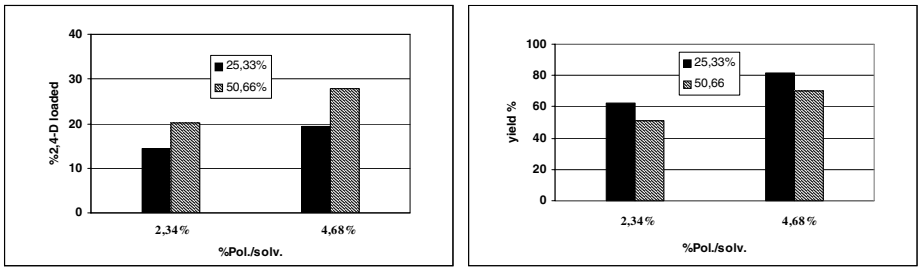


Figure 4: Effect of initial drug-polymer ratio (25.33% and 50.66%) on the mean values of 2,4-D loaded and encapsulation yield (%PVA=0.25%, N=300rpm pH=1.1; DCM/acetone) (number of measurements n=3).

In general, the effectiveness of the solvent evaporation method to produce microspheres depends on the successful entrapment of the active agent and encapsulation yield. Therefore , 2,4-D can be encapsulated using this technique with higher drug loading by combination of the three parameters, namely, aqueous phase pH, polymer-solvent ratio and organic phase solvent. In addition, the desired size can be obtained by varying stirring speed.

Herbicide release studies:

Figure 5 shows some examples of release profiles of 2,4-D in deionised water at pH=5.5 from ethylcellulose microspheres. In order to obtain meaningful information for the release model, we have tested the validity of the approached analytical solution (equation 4) of Fick's Law during the earlier stages. As shown in figure 6, the release

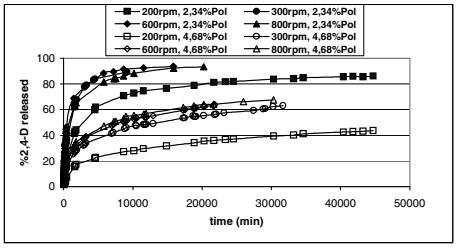


Figure 5: 2,4-D release profiles from ethyl cellulosemicrospheres(0.25%PVA,pH=5.5, 25.33%2,4-Di).

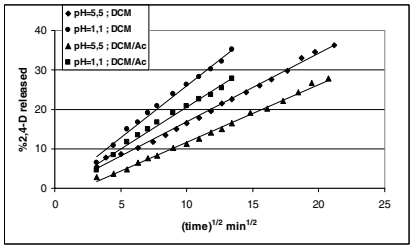


Figure 6: Fickien behaviour of 2,4-D released from microspheres (0.25%PVA, 2.34%Pol., 25.33%2,4-Di).

data have given straight line relation between the fractional release of 2,4-D and the square root of time. The R^2 values indicate a good fit at the short time of release (30-35% of drug released). From this we can say that the 2,4-D release mechanisms from microspheres are governed by diffusion process throughout microspheres according to Fick's laws [25].

In this part we report the results of work intended to link up the process control parameters of microencapsulation and the factors controlling the drug release. So, first we have noted above that stirring speed and polymer-solvent ratio give strong effect on particle size. In table2, we have reported values of release rates as function of process parameters; the release rate is expressed by Δ%2,4-D released/Δsquare root of time. We note that when the mean diameter has increased by decreasing stirring speed, the release rate decreases. In fact as following in figure 7, relationships have been obtained between release rate and the mean diameter of Sauter (D_{32}).

Table 2: Effects of some of the process parameters on the release rates.

Process parameters					**D_{32} (µm)**	**% 2,4-$D_{released}$ = f($t^{1/2}$)**	**R^2**	**t_{50} (min)**
%2,4-Di	%pol.	N (rpm)	Solvent	pH				
25.33	2.34	200	DCM	5.5	220.9	%2,4-D=1.102 $t^{1/2}$-0.8004	0.9787	2800
25.33	2.34	300	DCM	5.5	125.7	%2,4-D=1.7313 $t^{1/2}$-0.4869	0.9960	900
25.33	2.34	600	DCM	5.5	93.3	%2,4-D=2.6349 $t^{1/2}$-4.6347	0.9973	800
25.33	2.34	800	DCM	5.5	87.7	%2,4-D=2.7704 $t^{1/2}$-3.1391	0.9819	800
25.33	4.68	200	DCM	5.5	743.5	%2,4-D=0.470 $t^{1/2}$-3.0883	0.9961	-
25.33	4.68	300	DCM	5.5	422.4	%2,4-D=0.7597 $t^{1/2}$-1.014	0.9957	14000
25.33	4.68	600	DCM	5.5	283.6	%2,4-D=1.0507 $t^{1/2}$-0.7414	0.9854	8500
25.33	4.68	800	DCM	5.5	248.4	%2,4-D=1.264 $t^{1/2}$-1.3897	0.9898	7000
25.33	2.34	300	DCM/Ac	1.1	136.1	%2,4-D=2.109 $t^{1/2}$-0.4768	0.9881	2000
25.33	4.68	300	DCM/Ac	1.1	401.5	%2,4-D=0.5575 $t^{1/2}$+1.7456	0.9798	25900
50.66	2.34	300	DCM/Ac	1.1	129.6	%2,4-D=1.9784 $t^{1/2}$+17.471	0.9888	200
50.66	4.68	300	DCM/Ac	1.1	376.0	%2,4-D=0.5567 $t^{1/2}$+10.603	0.9830	12500

t_{50}: is time corresponding to 50% of drug released.

In all conditions, we have obtained slow release by increasing polymer-solvent ratio. Microspheres prepared using acetone as co-solvent discharged the drug with lower release rate; however, the ones prepared in acidic medium have given higher release rate (figure 6). As shown in figure 8, drug –polymer ratio did not affect the release rate but when it increased, we have obtained an important burst-effect. Indeed, microspheres prepared with 50.66% of drug-polymer ratio exhibit higher initial release. As shown in SEM micrographs, particles of solid 2,4-D are present on the surface of microspheres. Some examples of t_{50} are given in table 2; we note that this time can be increased by increasing the mean diameter and significantly by reducing drug-polymer ratio. At last, the remarks demonstrate that the process parameters control the release rate; then, we conclude that we have obtained controlled release formulations containing the herbicide 2,4-D, by solvent evaporation technique using ethylcellulose as matrix.

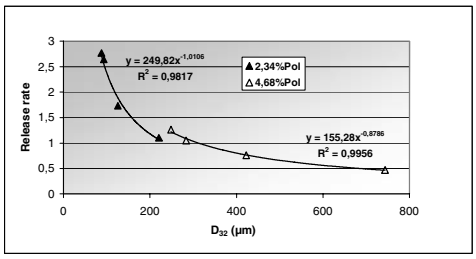


Figure 7: Effect of particle size on the pesticide release rate. (0.25%PVA, 25.33%2,4-D, DCM, pH=5.5).

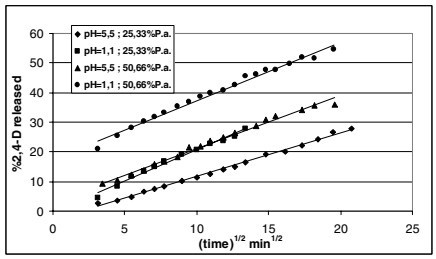


Figure 8: Effect of initial drug-polymer ratio on the pesticide release rate (0.25%PVA, 2.34%Pol. DCM/acetone).

Since, the soil pH can achieve alkaline values we have also studied the drug release in basic medium. The dissolution studies at pH=9.1 give the same profiles and release rates slightly fast than in pH=5.5. In this condition, the basic form of 2,4-D is preponderant and then it becomes more soluble .Therefore the drug discharge increases. Table 3 presents some of the values of fractional drug release as function of time.

Table 3: Results of 2,4-D released at pH=5.5 and pH=9.1 as function of time from batchs of microspheres.

		Time (min)							
		20	60	105	200	410	1520	3320	10100
Lot A	%2,4-D released at pH=5.5	11.6	19.0	22.0	27.8	38.5	63.3	79.0	91.2
	%2,4-D released at pH=9.1	11.8	19.7	23.7	31.8	50.2	79.1	96.3	99.0
Lot B	%2,4-D released at pH=5.5	8.5	16.7	20.7	27.7	34.1	47.8	57.5	67.1
	%2,4-D released at pH=9.1	13.8	23.5	30.3	36.9	45.3	59.7	70.2	81.1

Lot A: %PVA=0.25%, %Pol=2.34%, % p.a.=25.33% N=300rpm, pH=5.5, solvent: DCM.
Lot B: %PVA=0.25%, %Pol=2.34%, % p.a.=25.33%, N=300rpm, pH =1.1, solvent: DCM/acetone .

Conclusion

This controlled 2,4-D release system presents many advantages.
It is easy to manufacture it and we can handle it without risk. The active agent is protected from the external aggressions. The polymeric matrix is biodegradable and the herbicide release can be controlled.
We can choose the operating conditions in order to achieve the desired microspheres according to their utilisation . The drug entrapment can be improved especially by increasing polymer-solvent ratio or/and decreasing pH of continuous phase. The drug loading can increase from 7.7 to 27% by modifying the process parameters.
Particle size can be controlled absolutely by stirring speed and polymer-solvent ratio.
The release rate depends strongly on the particle size because we have demonstrated that drug liberation is governed by diffusion process throughout ethylcellulose microspheres.

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